

REMARKS

Claims 27-32 are pending in this application and were under examination in the Office Action dated October 27, 2008. Applicants note with appreciation that all previous rejections have been overcome. Two new rejections on the basis of enablement and obviousness over a new reference have been raised in the outstanding Office Action. These rejections are addressed individually below.

Claims 27-32 are Enabled by the Specification.

Claims 27-32 stand rejected under 35 U.S.C. §112, first paragraph on the basis that the specification, "while being enabling for the claimed method wherein the VEE-specific antibody is administered subsequent to VEE administration and infection," allegedly does not enable the method when the antibody and VEE are administered concurrently (Office Action, page 2, point 3). In particular, the Office Action states that Gould et al. (*J. Gen. Virol.* 70:1605-1608 1989)) teaches that enhancement of virulence could be induced only if the virus was allowed to first establish a productive infection in the mouse brain before the antibody was administered. The Office Action further states that "[t]he specification does not appear to disclose a working example where VEE and VEE-E1 or E2-specific monoclonal antibody was administered concurrently. Example 6 discloses that mice were infected with virus elements 3 weeks prior to administration of the monoclonal antibody." (Office Action at page 4, lines 1-4). This rejection is addressed below.

Claims 27-30 encompass administration of virus and antibody together or in any order, and claims 31 and 32 specifically recite "concurrent" administration. The Office Action alleges that the invention is only enabled for methods wherein the VEE specific antibody is administered after VEE administration and infection. The Applicants respectfully submit that the experiments in Example 6 have been mischaracterized in the Office Action.

As shown in Figure 7 and described in the first paragraph of Example 6, mice were inoculated with VRP pre-incubated with control or anti-VEE serum and the effect of each treatment on targeting VRP infection to dendritic cells was evaluated. Thus, this first study describes concurrent administration of virus and antibody. In the second paragraph of Example 6, a subsequent study is described to evaluate the effect of pre-existing anti-VEE

antibodies as a result of previous exposure to VEE. In this study, mice were inoculated with VRP expressing the influenza HA antigen and then three weeks later with VRP expressing GFP. By using different antigens, the effects of anti-VRP antibodies could be isolated. As shown in Figure 8, the results were similar to the first study and demonstrated a targeting of virus infection to dendritic cells. Thus, this second study describes virus administration after the presence of antibody has already been established in the animal. Although the VRP-HA virus was also administered three weeks previously, the VRP would not result in a productive, persistent infection.

In sum, Example 6 demonstrates concurrent administration of virus and antibody and administration of virus after an antibody response has been established.

Accordingly, in view of the foregoing, Applicants respectfully submit that the subject matter of claims 27-32 is enabled and respectfully request that the outstanding rejection under 35 U.S.C. §112, first paragraph be withdrawn.

The Claimed Subject Matter of Claims 27-30 is Nonobvious over Johnston et al. in view of Gould et al.

Claims 27-30 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 95/32733 (Johnston et al.) in view of Gould et al. (*J. Gen. Virol.* 70:1605-1608 1989)). The Office Action states that Johnston et al. teaches a method of administering a VEE virus that encodes and expresses a heterologous immunogen as a vaccine, but concedes that Johnston et al. does not teach administration of an antibody that specifically binds to the VEE E1 glycoprotein along with the VEE. The Office Action further states, however, that Gould et al. teaches antibody dependent enhancement of Yellow Fever and Japanese Encephalitis neurovirulence when monoclonal antibodies specific for the E glycoprotein were administered to the subject three days after administration of the virus, citing the abstract and Tables 1-3 of the Gould et al. reference. The Office Action concludes that it would have been obvious to one of ordinary skill in the art to combine the Johnston et al and Gould et al. references to administer E1 glycoprotein specific antibodies with a VEE that comprises a heterologous sequence, wherein the antibody is administered subsequent to administration of the VEE in order to enhance the infectivity of the VEE in a subject. This rejection is respectfully traversed below.

The teachings of Gould et al. can be readily distinguished from the present invention in that Gould et al. is focused on flaviviruses and not alphaviruses or, more specifically, VEE as recited by the present claims. One of ordinary skill in the art at the time of invention would have had no motivation with respect to the presently-claimed methods of administering VEE virus based on the disclosure in Gould et al. regarding flaviviruses. There certainly would have been no reasonable expectation of success that the antibody-dependent enhancement seen with these two flaviviruses would carry over to VEE, which is an alphavirus. Indeed, Gould et al. was unable to demonstrate antibody-dependent enhancement with West Nile Virus, louping ill Virus, Tick Borne Encephalitis, Murray Valley Encephalitis Virus, Dengue Virus and Montano Myotis Leukoencephalitis Virus (Gould et al., paragraph spanning pages 1606-1607). The failed studies described by Gould et al. underscore the uncertainty in transferring the results with one virus to another virus even within the same virus family (e.g., flaviviruses), much less to another virus family (e.g., alphaviruses). Clearly, based on the unpredictability of results within flaviviruses as reported by Gould et al., one of ordinary skill in the art would not have had any reasonable expectation of success in applying the teachings of Gould et al. to an alphavirus such as VEE.

In addition, the outstanding rejection fails to satisfy the requirements of a *prima facie* case of obviousness under *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, 127 S.Ct. 1727; 82 USPQ2d 1385 (2007) (*hereinafter*, "KSR"). Moreover, the outstanding rejection is not in compliance with the examination guidelines recently issued by the USPTO following the *KSR* decision for examining patent applications with respect to the nonobviousness requirement.

As stated in the "Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*" (72 Fed. Reg. 57526, October 10, 2007; *hereinafter* "the Examination Guidelines"), in *KSR* "the Supreme Court reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co.*..." (Examination Guidelines, Federal Register at page 57526). Hence, and as long established under that framework, to establish a *prima facie* case of obviousness, three requirements must be satisfied (M.P.E.P. § 2143). First, the prior art relied upon, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *In re Oetiker*,

24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the proposed modification or combination of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Third, the prior art reference or combination of references must teach or suggest all of the limitations of the claims. See *In re Wilson* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art").

It is accepted that the biotechnology arts, like the chemical arts, are less predictable than many other fields of inventive endeavor. The invention at issue in *KSR* was an adjustable gas-pedal system – an invention in the mechanical arts. The mechanical arts are generally recognized as relatively predictable as compared with the biotechnology or chemical arts. Indeed, the Federal Circuit recently articulated concerns regarding the application of the *KSR* holding to the chemical arts:

To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

Eisai Co. v. Dr. Reddy's Laboratories, July 21, 2008 --- F.3d ----, 2008 WL 2791884 (Fed. Cir. 2008) (*emphasis added*; copy enclosed). Likewise, potential solutions in the biotechnology arts are also unlikely "to be genuinely predictable."

In view of the decision in *KSR*, the USPTO issued the Examination Guidelines for examination of applications with respect to the nonobviousness requirement of 35 U.S.C. §103. The Examination Guidelines set out seven different "rationales" designated "A" to "G" for maintaining an obviousness rejection under *KSR*. Under all of these rationales and/or their factual underpinnings, the touchstones for obviousness are phrased in terms of "predictability" or "reasonable expectation of success" or both. Specifically, the seven rationales are, in relevant part (*emphasis added*):

A. Combining Prior Art Elements According to Known Methods to Yield Predictable Results based on articulation of the following findings:

(1) . . .

(2) . . .

(3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and

(4) . . .

B. Simple Substitution of One Known Element for Another to Obtain Predictable Results based on articulation of the following findings:

(1) . . .

(2) . . .

(3) a finding that one of ordinary skill in the art could have substituted one known element for another and the results of the substitution would have been predictable;

C. Use of Known Techniques to Improve Similar Devices (Method, or Product) in the Same Way based on articulation of the following findings:

(1) . . .

(2) . . .

(3) a finding that one of ordinary skill in the art could have applied the known "improvement" technique in the same way to the "base" device (method, or product) and the results would have been predictable to one of ordinary skill in the art; and

(4) . . .

D. Applying a Known Technique to a Known Device (Method, or Product) Ready for Improvement to Yield Predictable Results based on articulation of the following findings:

(1) . . .

(2) . . .

(3) a finding that one of ordinary skill in the art would have recognized that applying the known technique would have yielded predictable results and resulted in an improved system; and

(4) . . .

E. "Obviousness to Try" – Choosing from a Finite Number of Identified, Predictable Solutions, With a Reasonable Expectation of Success based on articulation of the following findings:

(1) . . .

(2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;

(3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and

(4) . . .

F. Known Work in One Field of Endeavor May Prompt Variations of it for Use in Either the Same Field or a Different One Based on Design Incentives or Other Market Forces if The Variations Would Have Been Predictable to One of Ordinary Skill in the Art.

(1) . . .

(2) . . .

(3) . . .

(4) a finding that one of ordinary skill in the art, in view of the identified design incentives or other market forces, could have implemented the claimed variation of the prior art, and the claimed variation would have been predictable to one of ordinary skill in the art; and

(5) . . .

G. Some Teaching, Suggestion, or Motivation in the Prior Art That Would Have Led One of Ordinary Skill to Modify the Prior Art Reference To Combine Prior Art Reference Teachings To Arrive at the Claimed Invention based on articulation of the following findings:

(1) . . .

(2) a finding that there was reasonable expectation of success; and

(3) . . .

Accordingly, to maintain an obviousness rejection under *KSR* (and the Examination Guidelines), the Examiner must provide adequate reasoning regarding the predictability

and reasonable expectation of success of the claimed invention by one of ordinary skill in the art in view of the prior art. In particular, the Examination Guidelines state that “[i]n short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the art would have known at the time of the invention, and on what such a person would have been reasonably expected to have been able to do in view of that knowledge.” (Federal Register at page 57527, top of third column; *emphasis added*). Further, the Examination Guidelines admonish: “Note that combining known prior art elements is not sufficient to render the claimed invention obvious if the result should not have been predictable to one of ordinary skill in the art.” (Federal Register at page 57529 (col. 3); *emphasis*).

In sum, under *KSR* the touchstones for the obviousness inquiry are predictability and reasonable expectation of success. As noted repeatedly by the USPTO, biotechnology is unpredictable. One of ordinary skill in the art would not have been motivated to carry out the present invention or a reasonable expectation in so doing based on Johnston et al. in view of Gould et al. Johnston et al. does not teach administration of an antibody that specifically binds to the E1 and/or E2 glycoprotein of the VEE vector to the subject. Gould et al. describes the unpredictable results observed with flaviviruses. In view of the uncertainty observed with flaviviruses, one of ordinary skill in the art at the time of invention would have had no motivation or reasonable expectation of success in carrying out the present invention with VEE, which is an alphavirus.

Further, Gould et al. were looking at a different end-point than the present inventors. Gould et al. were looking at antibody-dependent enhancement of neurovirulence by flaviviruses. This is more similar to the situation seen with Dengue virus in which antibody dependent enhancement leads to increased pathology (e.g., Dengue shock syndrome). In contrast, the present invention achieves antibody-dependent enhancement of the efficacy of VEE vectors and/or retargeting of the virus to antigen presenting cells (e.g., dendritic cells) in the absence of any significant increase in pathology (see, e.g., Specification at page 3, line 28 to page 4 line 3 and at page 7, line 25 to page 8, line 3). Thus, the disclosure by Gould et al. of antibody-dependent enhancement of neurovirulence by yellow fever virus would not have rendered the present invention obvious in which antibody-dependent enhancement results in enhanced efficacy


of VEE vectors and/or retargeting of VEE vectors to antigen-presenting cells and does not result in significantly increased pathology.

In sum, Applicants respectfully submit that the subject matter of claims 27-32 is novel and nonobvious over Johnston et al. in view of Gould et al. and respectfully request that the rejection under 35 U.S.C. 103(a) over the combination of these references be withdrawn.

Conclusion.

Having addressed all of the issues raised by the Examiner in the pending Office Action, Applicants respectfully request the withdrawal of the pending rejections and allowance of the pending claims to issue. Should the Examiner have any remaining concerns, it is respectfully request that the Examiner contact the undersigned attorney to expedite the prosecution of this application to allowance.

Respectfully submitted,


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